Affiliated Genetics
2749 East Parleys Way, Suite 100
Salt Lake City, UT 84109
CLIA ID: 46D1077919

Affiliated Pharmarisk Basic Created for:

Patient:
HIPAA Compliant Fax:
Physician:
Address:
Collection Date:
Specimen Type:

Accession #:
Gender:
DOB:
Received Date:
Report Generated:

Key Test Findings

Pharmacogenetic Results

	Assay	Results	Phenotype	Clinical Consequences
	CYP2C19	*1/*17	Rapid Metabolizer	Consistent with a significant increase in CYP2C19 activity. Potential risk for side effects or loss of efficacy with drug substrates.
	CYP2C9	*1/*1	Normal Metabolizer	Consistent with a typical CYP2C9 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
	CYP2D6	*4/*4 XN	Poor Metabolizer	Consistent with a significant deficiency in CYP2D6 activity. Increased risk for side effects or loss of efficacy with drug substrates.
	VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity	VKORC1 is the site of action of warfarin. The patient may require a decrease in warfarin dosage.

Medication Guidance

Psychotropic Medications

Standard Precautions	Use With Caution	Consider Alternatives
Bupropion (Wellbutrin)	Amphetamine (Adderall)	Amitriptyline (Elavil)
Clobazam (Onfi)	Aripiprazole (Abilify)	Citalopram (Celexa)
Desvenlafaxine (Pristiq)	Atomoxetine (Strattera)	Clomipramine (Anafranil)
Fosphenytoin (Cerebyx)	Clozapine (Clozaril)	Desipramine (Norpramin)
Gabapentin (Neurontin)	Dexmethylphenidate (Focalin)	Doxepin (Silenor)
Lorazepam (Ativan)	Dextroamphetamine (Dexedrine)	Escitalopram (Lexapro)
Mirtazapine (Remeron)	Diazepam (Valium)	Haloperidol (Haldol)
Naltrexone (Vivitrol)	Donepezil (Aricept)	Imipramine (Tofranil)
Oxazepam (Serax)	Duloxetine (Cymbalta)	Nortriptyline (Pamelor)
Paliperidone (Invega)	Galantamine (Razadyne)	Risperidone (Risperdal)
Phenytoin (Dilantin)	Iloperidone (Fanapt)	Thioridazine (Mellaril)
Pregabalin (Lyrica)	Lisdexamfetamine (Vyvanse)	Trimipramine (Surmontil)
Sertraline (Zoloft)	Methylphenidate (Ritalin)	Venlafaxine (Effexor)
	Olanzapine (Zyprexa)	
	Paroxetine (Paxil)	
	Perphenazine (Trilafon)	
	Pimozide (Orap)	
	Tetrabenazine (Xenazine)	
	Vortioxetine (Brintellix)	

Cardiovascular Medications

Standard Precautions	Use With Caution	Consider Alternatives
Atorvastatin (Lipitor)	Carvedilol (Coreg)	Metoprolol (Lopressor)
Fluvastatin (Lescol)	Clopidogrel (Plavix)	
Irbesartan (Avapro)	Flecainide (Tambocor)	
Lovastatin (Mevacor)	Mexiletine (Mexitil)	
Nebivolol (Bystolic)	Propafenone (Rythmol)	
Pitavastatin (Livalo)	Timolol (Timoptic)	
Prasugrel (Effient)	Warfarin (Coumadin)	
Pravastatin (Pravachol)		
Propranolol (Inderal)		
Rosuvastatin (Crestor)		
Simvastatin (Zocor)		
Ticagrelor (Brilinta)		

Pain Medications

Standard Precautions	Use With Caution	Consider Alternatives
Buprenorphine (Butrans, Buprenex)	Carisoprodol (Soma)	Codeine (Codeine)
Celecoxib (Celebrex)	Fentanyl (Actiq)	Tramadol (Ultram)
Cyclobenzaprine (Flexeril, Amrix)	Hydrocodone (Vicodin)	
Dihydrocodeine (Synalgos-DC)	Methadone (Dolophine)	
Flurbiprofen (Ansaid)	Morphine (MS Contin)	
Hydromorphone (Dilaudid, Exalgo)	Oxycodone (Percocet)	
Meperidine (Demerol)	Tizanidine (Zanaflex)	
Oxymorphone (Opana, Numorphan)		
Piroxicam (Feldene)		
Tapentadol (Nucynta)		

Other Medications

Standard Precautions	Use With Caution	Consider Alternatives
Fesoterodine (Toviaz)	Darifenacin (Enablex)	
Glimepiride (Amaryl)	Dexlansoprazole (Dexilant)	
Glipizide (Glucotrol)	Esomeprazole (Nexium)	
Glyburide (Micronase)	Lansoprazole (Prevacid)	
Mirabegron (Myrbetriq)	Metoclopramide (Reglan)	
Ondansetron (Zofran)	Omeprazole (Prilosec)	
Rabeprazole (Aciphex)	Pantoprazole (Protonix)	
Tolbutamide (Orinase)	Tacrolimus (Prograf)	
	Tamsulosin (Flomax)	
	Tolterodine (Detrol)	
	Voriconazole (Vfend)	

PharmaRisk™ Basic

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Test Details

Gene	Alleles Tested
CYP2C19	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *12, *17
CYP2C9	*2, *3, *4, *5, *6, *8, *10, *11, *12, *13, *15, *25, *27
CYP2D6	*2, *3, *4, *4M, *6, *7, *8, *10, *11, *12, *14A, *14B, *15, *17, *18, *19, *20, *29, *35, *38, *41, *44, *56, *5 (gene deletion), XN (gene duplication)
VKORC1	1542G>C, -1639G>A, 1173C>T

Methodology:

Testing is performed on DNA extracted from a buccal swab. Samples are genotyped using Taqman® allele discrimination assays. The assays detect alleles listed above, including all common and most rare variants with known clinical significance at analytical sensitivity and specificity >99%.

Limitations:

The interpretations provided in this report are provided to assist health care providers, but they are not a treatment recommendation. Diagnosis and treatment remain the sole responsibility of the ordering physician. While the polymorphisms tested are important, other variants and mutations in these genes will not be detected. Mutations in other genes that could affect drug metabolism will not be detected. Non-genetic factors also affect metabolism. This test is not a substitute for clinical and therapeutic drug monitoring. This report does not address patient drug allergies or drug-drug interactions.

Signature:

Kenneth Ward m.d.

Kenneth Ward M.D.

Date: 6/25/2014

CLIA FDA Statement:

This Laboratory Developed Test was developed and its performance characteristics determined by Affiliated Genetic, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing and has established and verified the test's accuracy. This test has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. These results are adjunctive to an ordering physician's diagnosis.

Appendix: Dosing Guidance

Amitriptyline (Elavil)

Increased Sensitivity to Amitriptyline (CYP2C19 *1/*17 Rapid Metabolizer)

Consider an alternative drug or consider prescribing amitriptyline at standard dose and monitor the plasma concentrations of amitriptyline and nortriptyline to guide dose adjustments.

Amitriptyline (Elavil)

Increased Sensitivity to Amitriptyline (CYP2D6 *4/*4 XN Poor Metabolizer)

Select an alternative drug or consider prescribing amitriptyline at a reduced dose (50% reduction) with monitoring of plasma concentrations of amitriptyline and nortriptyline.

Amphetamine (Adderall)

Poor Response to Amphetamine salts (COMT Val158Met AA Low COMT Activity)

The patient's genotype predicts a reduced therapeutic response to amphetamine stimulants. If prescribed, amphetamines should be administered at the lowest effective dose and dosage should be individually adjusted.

Aripiprazole (Abilify)

Increased Sensitivity to Aripiprazole (CYP2D6 *4/*4 XN Poor Metabolizer)

Aripiprazole dose should initially be reduced to one-half (50%) of the usual dose and then adjusted to achieve a favorable clinical response. Reduce the maximum dose to 10 mg/day (67% of the maximum recommended daily dose). The dose of aripiprazole for poor metabolizers patients who are administered a strong CYP3A4 inhibitor should be reduced to one-quarter (25%) of the usual dose.

Atomoxetine (Strattera)

Increased Sensitivity to Atomoxetine (CYP2D6 *4/*4 XN Poor Metabolizer)

Careful titration is recommended with monitoring for toxicity until a favorable response is achieved. In children and adolescents up to 70 kg body weight, atomoxetine should be initiated at standard dosing of 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. In children and adolescents over 70 kg body weight and adults, atomoxetine should be initiated at standard dosing of 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

Carisoprodol (Soma)

Altered Sensitivity to Carisoprodol (CYP2C19 *1/*17 Rapid Metabolizer)

There is insufficient data to allow calculation of dose adjustment and if carisodoprol is prescribed, it is recommended to use a lower dose and to carefully monitor the patient for side effects.

Carvedilol (Coreg)

Moderate Sensitivity to Carvedilol (CYP2D6 *4/*4 XN Poor Metabolizer)

Carvedilol can be prescribed at standard label recommended-dosage and administration. CYP2D6 poor metabolizers may experience dizziness during up-titration. Careful titration is recommended with monitoring until a favorable response is achieved.

Citalopram (Celexa)

Insufficient Response to Citalopram (CYP2C19 *1/*17 Rapid Metabolizer)

The patient may not respond to usual doses. Monitor plasma concentration and increase dose to a maximum of 150% in response to efficacy and adverse events or select alternative drug.

Clomipramine (Anafranil)

Increased Sensitivity to Clomipramine (CYP2C19 *1/*17 Rapid Metabolizer)

Consider an alternative drug or consider prescribing clomipramine at standard dose and monitor the plasma concentrations of clomipramine and desmethyl-clomipramine to guide dose adjustments.

Clomipramine (Anafranil)

Increased Sensitivity to Clomipramine (CYP2D6 *4/*4 XN Poor Metabolizer)

Consider alternative or prescribe clomipramine at 50% of recommended standard starting dose. Monitor plasma concentrations of clomipramine and desmethylclomipramine and titrate accordingly until a favorable response is achieved.

Clopidogrel (Plavix)

Increased Response to Clopidogrel (CYP2C19 *1/*17 Rapid Metabolizer)

Clopidogrel can be prescribed at standard label-recommended dosage. Individuals with the *17 allele may have an increased risk of bleeding while taking clopidogrel.

Clozapine (Clozaril)

Unknown Response to Clozapine (CYP1A2 *1V/*1V Unknown Phenotype)

Although the patient's CYP1A2 metabolism status cannot be predicted accurately, smoking may increase the risk of non-response to standard doses. There is an association between high clozapine doses and the risk of seizures, therefore careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels leading to adverse events and therapeutic drug monitoring accompanied by dose reduction is recommended in patients who have quit smoking.

Codeine (Codeine)

Non-Response to Codeine (CYP2D6 *4/*4 XN Poor Metabolizer)

Greatly reduced morphine levels are expected and the patient may not experience adequate pain relief when taking codeine. Avoid prescribing codeine and consider alternative opioids other than tramadol or consider a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: Fentanyl, Morphine, Hydromorphone, Oxymorphone and Tapentadol.

Darifenacin (Enablex)

Possible Sensitivity to Darifenacin (CYP2D6 *4/*4 XN Poor Metabolizer)

Darifenacin exposure is increased 30% in CYP2D6 poor metabolizers. Although no dose adjustment may not be needed in these patients, monitor patients for increased side effects when darifenacin is prescribed at standard label recommended-dosage and administration.

Desipramine (Norpramin)

Increased Sensitivity to Desipramine (CYP2D6 *4/*4 XN Poor Metabolizer)

Consider alternative or prescribe desipramine at 50% of recommended standard starting dose. Monitor plasma concentrations of desipramine and metabolites and titrate accordingly until a favorable response is achieved.

Dexlansoprazole (Dexilant)

Possible Insufficient Response to Dexlansoprazole (CYP2C19 *1/*17 Rapid Metabolizer)

Be alert to insufficient response and **consider dose increase**. There is insufficient data to allow calculation of dose adjustment.

Dexmethylphenidate (Focalin)

Poor Response to Dexmethylphenidate (COMT Val158Met AA Low COMT Activity)

The patient's genotype predicts a reduced therapeutic response to dexmethylphenidate. Dosage should be individualized according to the needs and responses of the patient. Therapy should be initiated in small doses, with gradual weekly increments.

Dextroamphetamine (Dexedrine)

Poor Response to Dextroamphetamine (COMT Val158Met AA Low COMT Activity)

The patient's genotype predicts a reduced therapeutic response to amphetamine stimulants. If prescribed, dextroamphetamine should be administered at the lowest effective dose and dosage should be individually adjusted.

Diazepam (Valium)

Altered Sensitivity to Diazepam (CYP2C19 *1/*17 Rapid Metabolizer)

There is insufficient data to allow calculation of dose adjustment when diazepam is prescribed. Monitor the response and adjust the dose accordingly or select an alternative drug.

Donepezil (Aricept)

Possible Altered Response to Donepezil (CYP2D6 *4/*4 XN Poor Metabolizer)

When compared to a normal metabolizer, a poor metabolizers has a 30% decrease in donepezil clearance; the clinical significance of this decrease is not well documented. Consider using a standard dosing regimen and be alert for adverse events and adjust dosage in response to clinical response and tolerability.

Doxepin (Silenor)

Increased Sensitivity to Doxepin (CYP2C19 *1/*17 Rapid Metabolizer)

Consider an alternative drug or consider prescribing doxepin at standard dose and monitor the plasma concentrations of doxepin and desmethyl-doxepin to guide dose adjustments.

Doxepin (Silenor)

Increased Sensitivity to Doxepin (CYP2D6 *4/*4 XN Poor Metabolizer)

Consider alternative drug or reduce doxepin starting dose by 50%. Adjust maintenance dose according to nordoxepin plasma concentrations.

Duloxetine (Cymbalta)

Possible Sensitivity to Duloxetine (CYP2D6 *4/*4 XN Poor Metabolizer)

Limited data suggest that duloxetine plasma concentrations might be increased in poor metabolizers of CYP2D6, therefore duloxetine can be prescribed at standard label recommended-dosage and careful titration is recommended until a favorable response is achieved.

Escitalopram (Lexapro)

Insufficient Reponse to Escitalopram (CYP2C19 *1/*17 Rapid Metabolizer)

Monitor plasma concentration and titrate dose to a maximum of 150% in response to efficacy and adverse events or select alternative drug.

Esomeprazole (Nexium)

Insufficient Response to Esomeprazole (CYP2C19 *1/*17 Rapid Metabolizer)

- Helicobacter pylori eradication: increase dose by 50-100% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase by 50-100%.

Fentanyl (Actiq)

Altered Response to Fentanyl (OPRM1 A118G AG Altered OPRM1 Function)

The patient carries one copy of the OPRM1 118A>G mutation. Acute postoperative and cancer pain: the patient's genotype has been shown to be associated with reduced analgesia at standard fentanyl doses. Therefore the patient may require higher doses of this drug. Because fentanyl has a narrow therapeutic window, it is advised to carefully titrate this drug to a tolerable dose that provides adequate analgesia with minimal side effects.

Flecainide (Tambocor)

Significantly Increased Sensitivity to Flecainide (CYP2D6 *4/*4 XN Poor Metabolizer)

Consider prescribing a lower flecainide dose. When compared to a CYP2D6 normal metabolizer, a poor metabolizer may require a 50% dose reduction.Careful titration with ECG recording and monitoring of flecainide plasma concentrations are recommended until a favorable clinical response is achieved.

Galantamine (Razadyne)

Possible Sensitivity to Galantamine (CYP2D6 *4/*4 XN Poor Metabolizer)

A CYP2D6 poor metabolizer has a drug exposure that is approximately 50% higher than the exposure in a normal metabolizer. Although, dosage adjustment is not necessary in a patient identified as a CYP2D6 poor metabolizer as the dose of drug is individually titrated to tolerability, a slower titration can be considered as it may improve tolerability.

Haloperidol (Haldol)

Increased Sensitivity to Haloperidol (CYP2D6 *4/*4 XN Poor Metabolizer)

Consider alternative drug or prescribe haloperidol at 50% of the usual starting dose and then adjust dosage to achieve a favorable clinical response. Be alert to increased haloperidol plasma concentrations.

Hydrocodone (Vicodin)

Possible Altered Response to Hydrocodone (CYP2D6 *4/*4 XN Poor Metabolizer)

Decreased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 poor metabolizers. However, there is insufficient evidence as to whether poor metabolizers have decreased analgesia when taking hydrocodone. Adequate pain relief can be achieved by increasing the dose in response to pain symptoms. Other opioids not metabolized by CYP2D6 may also be considered (i.e. morphine, oxymorphone, buprenorphine, fentanyl, methadone and hydromorphone).

Hydrocodone (Vicodin)

Altered Response to Hydrocodone (OPRM1 A118G AG Altered OPRM1 Function)

Acute postoperative and cancer pain: the patient's genotype has been shown to be associated with reduced analgesia and increased opioid side effects at standard or high hydrocodone doses. If the patient fails to respond to increased hydrocodone doses, an alternative opioid may be considered.

Iloperidone (Fanapt)

Increased Sensitivity to Iloperidone (CYP2D6 *4/*4 XN Poor Metabolizer)

Iloperidone **dose should be reduced by one-half and titrate slowly to avoid orthostatic hypotension**. Because iloperidone is associated with QTc prolongation, caution is warranted when prescribing the drug in patients with reduced CYP2D6 activity. If patients taking iloperidone experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, including cardiac monitoring.

Imipramine (Tofranil)

Increased Sensitivity to Imipramine (CYP2C19 *1/*17 Rapid Metabolizer)

Consider an alternative drug or consider prescribing imipramine at standard dose and monitor the plasma concentrations of imipramine and desipramine to guide dose adjustments.

Imipramine (Tofranil)

Increased Sensitivity to Imipramine (CYP2D6 *4/*4 XN Poor Metabolizer)

Consider alternative drug or consider a 50% reduction of imipramine recommended starting dose and then titrate in response to imipramine and desipramine plasma concentrations.

Lansoprazole (Prevacid)

Insufficient Response to Lansoprazole (CYP2C19 *1/*17 Rapid Metabolizer)

- Helicobacter pylori eradication: increase dose by 200% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase by 200%.

Lisdexamfetamine (Vyvanse)

Poor Response to Lisdexamfetamine (COMT Val158Met AA Low COMT Activity)

The patient's genotype predicts a reduced therapeutic response to amphetamine stimulants. If prescribed, lisdexamfetamine should be administered at the lowest effective dose and dosage should be individually adjusted.

Methadone (Dolophine)

Unknown Sensitivity to Methadone (CYP2B6 Indeterminate Unknown Phenotype)

Until additional information is available, prescribe methadone with careful monitoring. If a genotype effect is suspected based on the patient response, adjust dosage accordingly or prescribe an alternative medication.

Methylphenidate (Ritalin)

Poor Response to Methylphenidate (COMT Val158Met AA Low COMT Activity)

The patient's genotype predicts a reduced therapeutic response to methylphenidate. Dosage should be individualized according to the needs and responses of the patient. Therapy should be initiated in small doses, with gradual weekly increments.

Metoclopramide (Reglan)

Increased Sensitivity to Metoclopramide (CYP2D6 *4/*4 XN Poor Metabolizer)

Metoclopramide is metabolized at a slower rate in CYP2D6 poor metabolizers; this results in significantly higher serum concentrations of the drug. Considering the CNS and extrapyramidal adverse effects of metoclopramide, close monitoring for toxicity and eventually a dose decrease are recommended. Patients with renal disease at increased risk.

Metoprolol (Lopressor)

Significantly Increased Sensitivity to Metoprolol (CYP2D6 *4/*4 XN Poor Metabolizer)

Based on the genotype result, this patient is at risk of experiencing excessive beta-blockade when taking metoprolol at standard dosage. Heart Failure: Consider alternative beta-blockers such as bisoprolol or carvedilol or prescribe metoprolol at a lower dose. When compared to a normal metabolizer, a poor metabolizer may require 75% dose reduction. Other indications: Consider alternative beta-blockers such as bisoprolol or atenolol or prescribe metoprolol at a lower dose. When compared to a normal metabolizer, a poor metabolizer may require 75% dose reduction. If metoprolol is prescribed, be alert to adverse events (e.g. bradycardia, cold extremities).

Mexiletine (Mexitil)

Significantly Increased Sensitivity to Mexiletine (CYP2D6 *4/*4 XN Poor Metabolizer)

Consider prescribing a lower mexiletine dose. A slow titration with ECG recording and monitoring of mexiletine plasma concentrations are recommended until a favorable clinical response is achieved.

Morphine (MS Contin)

Altered Response to Morphine (COMT Val158Met AA Low COMT Activity)

The patient carries two COMT Val158Met mutations, which translates to a reduced COMT function. The patient may require lower doses of morphine for adequate pain control. Dosing regimen needs to be individualized for each patient, taking into account the patient's prior analgesic treatment experience.

Nortriptyline (Pamelor)

Increased Sensitivity to Nortriptyline (CYP2D6 *4/*4 XN Poor Metabolizer)

Select an alternative drug or consider prescribing nortriptyline at a reduced dose (50% reduction) with monitoring of plasma concentrations of nortriptyline and metabolites.

Olanzapine (Zyprexa)

Unknown Response to Olanzapine (CYP1A2 *1V/*1V Unknown Phenotype)

There is little evidence regarding the impact of CYP1A2 genetic variants on olanzapine response. Although the patient's CYP1A2 metabolism status cannot be predicted accurately, smoking may increase the risk of non-response to standard doses and careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels leading to adverse events and therapeutic drug monitoring accompanied by dose reduction may be needed in patients who have quit smoking.

Omeprazole (Prilosec)

Insufficient Response to Omeprazole (CYP2C19 *1/*17 Rapid Metabolizer)

- Helicobacter pylori eradication: increase dose by 100-200% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase by 100-200%.

Oxycodone (Percocet)

Possible Altered Response to Oxycodone (CYP2D6 *4/*4 XN Poor Metabolizer)

Decreased conversion of oxycodone to the more active metabolite oxymorphone is expected in CYP2D6 poor metabolizers. However, there is insufficient evidence as to whether poor metabolizers have decreased analgesia when taking oxycodone. Adequate pain relief can be achieved by increasing the dose in response to pain symptoms. Other opioids not metabolized by CYP2D6 may also be considered (i.e. morphine, oxymorphone, buprenorphine, fentanyl, methadone and hydromorphone).

Pantoprazole (Protonix)

Insufficient Response to Pantoprazole (CYP2C19 *1/*17 Rapid Metabolizer)

- Helicobacter pylori eradication: increase dose by 400% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase by 400%.

Paroxetine (Paxil)

Possible Sensitivity to Paroxetine (CYP2D6 *4/*4 XN Poor Metabolizer)

At standard label-recommended dosage, paroxetine levels are expected to be high. Careful titration is recommended until a favorable response is achieved. When compared to a CYP2D6 normal metabolizer, a poor metabolizer may require a 50% dose reduction.

Perphenazine (Trilafon)

Increased Sensitivity to Perphenazine (CYP2D6 *4/*4 XN Poor Metabolizer)

Patients with a decreased CYP2D6 function will eliminate perphenazine more slowly which can result in higher drug concentrations and possibly higher adverse events (extrapyramidal symptoms). Consider close monitoring and dose reduction to avoid toxicity.

Pimozide (Orap)

Increased Sensitivity to Pimozide (CYP2D6 *4/*4 XN Poor Metabolizer)

The pimozide concentrations observed in poor CYP2D6 metabolizers are expected to be high and the time to achieve steady state pimozide concentrations is expected to be long (approximately 2 weeks). Consequently, CYP2D6 poor metabolizers are at an increased risk of QT prolongation at standard doses of pimozide. In CYP2D6 poor metabolizers, pimozide doses should not exceed 4 mg/day in adults or 0.05 mg/kg/day in children, and doses should not be increased earlier than 14 days.

Propafenone (Rythmol)

Increased Sensitivity to Propafenone (CYP2D6 *4/*4 XN Poor Metabolizer)

Consider reducing the propafenone dose and monitor ECG. Compared to normal metabolizers, poor metabolizers may require a 70% dose reduction. Consider monitoring for plasma concentrations.

Risperidone (Risperdal)

Significantly Increased Sensitivity to Risperidone (CYP2D6 *4/*4 XN Poor Metabolizer)

Consider alternative drug or prescribe risperidone at a reduced dose and be extra alert of adverse events and adjust dosage in response to clinical response and tolerability.

Tacrolimus (Prograf)

Hyporesponder to Tacrolimus (CYP3A5 *1/*7 Intermediate Metabolizer)

Studies have shown patients with a this genotype may be at increased risk for acute transplant rejection while taking a standard dose of tacrolimus. Therefore a tacrolimus dose increase with close monitoring are strongly recommended to achieve therapeutic effect.

Tamsulosin (Flomax)

Increased Sensitivity to Tamsulosin (CYP2D6 *4/*4 XN Poor Metabolizer)

Tamsulosin is metabolized at a slower rate in CYP2D6 poor metabolizers; this results in significantly higher serum concentrations of tamsulosin. Therefore, this drug should be used with caution in patients known to be CYP2D6 poor metabolizers, particularly at a daily dose higher than 0.4 mg.

Tetrabenazine (Xenazine)

Increased Sensitivity to Tetrabenazine (CYP2D6 *4/*4 XN Poor Metabolizer)

Individualization of dose with careful weekly titration is required. The first week's starting dose is 12.5 mg daily; second week, 25 mg (12.5 mg twice daily); then slowly titrate at weekly intervals by 12.5 mg to a tolerated dose. **The maximum daily dose in CYP2D6 poor metabolizers is 50 mg with a maximum single dose of 25 mg.** If serious adverse events occur, titration should be stopped and the dose of tetrabenazine should be reduced. If the adverse event(s) do not resolve, consider withdrawal of tetrabenazine.

Thioridazine (Mellaril)

Increased Sensitivity to Thioridazine (CYP2D6 *4/*4 XN Poor Metabolizer)

Reduced cytochrome CYP2D6 activity results in elevated plasma levels of thioridazine and would be expected to augment the prolongation of the QTc interval associated with thioridazine and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as Torsades de pointes type arrhythmias. Such an increased risk may result also from the additive effect of coadministering thioridazine with other agents that prolong the QTc interval. Therefore, thioridazine is contraindicated in patients with reduced levels of CYP2D6 activity.

Timolol (Timoptic)

Increased Sensitivity to Timolol (CYP2D6 *4/*4 XN Poor Metabolizer)

Potentiated systemic beta-blockade (e.g., bradycardia) has been reported during timolol treatment by patients with decreased CYP2D6 activity. Monitor patient for treatment-related adverse effects.

Tizanidine (Zanaflex)

Unknown Response to Tizanidine (CYP1A2 *1V/*1V Unknown Phenotype)

There is little evidence regarding the impact of CYP1A2 genetic variants on tizanidine response. Although the patient's CYP1A2 metabolism status cannot be predicted accurately, smokers may be at risk for non-response and may require higher doses. There is an association between high tizanidine plasma concentrations and the risk of hypotension and excessive sedation, therefore careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels leading to excessive hypotension and sedation. Careful monitoring accompanied by dose reduction may be needed in patients who have quit smoking.

Tolterodine (Detrol)

Possible Sensitivity to Tolterodine (CYP2D6 *4/*4 XN Poor Metabolizer)

Tolterodine is metabolized at a slower rate in CYP2D6 poor metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of its active metabolite (5-hydroxymethytolterodine). Considering the antimuscarinic potency of tolterodine and its active metabolite and the protein binding of these compounds, tolterodine accounts for the major part of the clinical effect in poor metabolizers and the same dosage can be applied irrespective of phenotype status.

Patients with Congenital or Acquired QT Prolongation: The effect of tolterodine on the QT interval prolongation is greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and is more pronounced in CYP2D6 poor metabolizers than normal metabolizers. This should be considered when tolterodine is prescribed to patients with a known history of QT prolongation or patients who are taking Class IA or Class III antiarrhythmics.

Tramadol (Ultram)

Non-Response to Tramadol (CYP2D6 *4/*4 XN Poor Metabolizer)

The patient will not experience adequate pain relief when taking tramadol. Avoid prescribing tramadol and consider alternative opioids other than codeine or consider a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: Fentanyl, Morphine, Hydromorphone, Oxymorphone and Tapentadol.

Trimipramine (Surmontil)

Increased Sensitivity to Trimipramine (CYP2C19 *1/*17 Rapid Metabolizer)

Consider an alternative drug or consider prescribing trimipramine at standard dose and monitor the plasma concentrations of trimipramine and desmethy-ltrimipramine to guide dose adjustments.

Trimipramine (Surmontil)

Increased Sensitivity to Trimipramine (CYP2D6 *4/*4 XN Poor Metabolizer)

Consider alternative drug or consider a 50% reduction of trimipramine recommended starting dose and then titrate in response to trimipramine plasma concentrations.

Venlafaxine (Effexor)

Significantly Increased Sensitivity to Venlafaxine (CYP2D6 *4/*4 XN Poor Metabolizer)

The patient has an increased risk of experiencing side effects when taking standard doses of venlafaxine. Consider alternative drug or prescribe venlafaxine and be extra alert of adverse events and adjust dosage in response to clinical response and tolerability. Monitor O-desmethylvenlafaxine plasma concentrations.

Voriconazole (Vfend)

Non-response to Voriconazole (CYP2C19 *1/*17 Rapid Metabolizer)

Voriconazole plasma concentrations may be low when standard dosage is used, increasing the risk of loss of response and effectiveness. Closely monitor voriconazole plasma concentrations and adjust the dose accordingly.

Vortioxetine (Brintellix)

Increased Sensitivity to Vortioxetine (CYP2D6 *4/*4 XN Poor Metabolizer)

CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive, carboxylic acid metabolite, and CYP2D6 poor metabolizers of CYP2D6 have approximately twice the vortioxetine plasma concentration of normal metabolizers. **Vortioxetine starting dose should be reduced by one-half. The maximum recommended dose is 10 mg/day in known CYP2D6 poor metabolizers.** Consider 5 mg/day for patients who do not tolerate higher doses.

Warfarin (Coumadin)

Normal Sensitivity to Warfarin (CYP2C9 *1/*1 VKORC1 -1639G>A G/A)

Initiation Therapy: consider using the following standard warfarin dose range as provided in the FDA-approved label: **5-7 mg/day**. OR consider using a personalized dose calculated by a pharmacogenetic algorithm. The estimated time to reach steady-state is 4 to 5 days.

PharmaRisk™ Basic

Affiliated Genetics

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CLIA ID: 46D1077919

Prescription Alert

DOB

This individual has been tested for gene variants that may affect medications prescribed.

GENE	RESULT
CYP2C19	Rapid Metabolizer
CYP2C9	Normal Metabolizer
CYP2D6	Poor Metabolizer
VKORC1	Intermediate Warfarin Sensitivity

Healthcare Providers: For up-to-date information concerning the impact of these genetic tests on drug precribing by may consult the PharmGKB database:

www.pharmgkb.org

Note:This patient has also been tested for common variants in the Factor II, Factor V, MTHFR, and ApoE genes.These results are available on the patient's medical records.